Shortening the path to Rare Disease diagnosis by using new born genetic screening and digital technologies

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

Topic details

Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Innovative medicines
IMI2 Strategic Research Agenda - Health Priority	Rare/orphan diseases

Specific challenges to be addressed by public-private collaborative research

Unmet medical need:

There are over 7000 rare diseases (RDs) resulting in 30 million patients in Europe and 250 million globally. Less than 10% of RD patients receive treatment and only 1% are managed using an approved treatment in Europe[1,2]. Delivering effective treatments to RD patients where the prevalence is low, has been described as one of the major global health challenges for the 21st century. There is a need for a strategic approach to address some of the major challenges faced by the RD Community, endorsed by IMI2 JU.

Challenges:

Even though RDs span across a plethora of multisystemic syndromes, involving virtually every single organ or physiological function, most RD patients face common problems. These major hurdles can be summarised as delayed diagnosis, lack of R&D, and lack of access to or reimbursement of innovative medicines[3].

One of the main challenges for RDs is related to diagnosis because RDs are characterised by a broad diversity of syndromic disorders and symptoms that vary from disease to disease and from patient to patient suffering from the same disease. In isolation, these symptoms can be very common, leading to misdiagnosis. Altogether, this leads to a lengthy and burdensome path to diagnosis that can on average take eight (8) years[4,5], often superposed with pointless treatments, and creates a heavy human and societal burden that could be avoided by earlier diagnosis.

Benefit to Public Health:

Early detection of rare genetic diseases would enable early intervention (when available), follow-up, and genetic counselling (such as family planning). This would result in improved clinical and patient oriented outcomes. Overall, this project will increase public understanding around RDs, and therefore foster rare disease R&D. A better

[1] https://globalgenes.org/2009/02/27/rare-disease-facts-and-figures/
[2] https://www.eurordis.org/about-rare-diseases
[3] https://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf
[4] https://globalgenes.org/2009/02/27/rare-disease-facts-and-figures/
[5] http://download2.eurordis.org.s3.amazonaws.com/documents/pdf/Undiagnosed-International-Joint-Recommendations.pdf

understanding of rare diseases would also potentially lead to better rare disease policies, as well as reduced healthcare inefficiencies & disparities.

Public Funding:

Strategic collaboration with Public Partners is required as this programme is at the cusp of Public Health Policy. To address the challenges and undertake a project of such a transformational nature, an active partnership from a range of contributors across the public and private sectors is necessary. A project of this nature and scope requires a synergistic effort across academia, industry partners and other relevant stakeholders, in order to potentially positively impact the lives of up to 30 million RD patients in the EU and their families. As mentioned above, RDs are diverse and complex, which calls for a vast and diverse group of collaborators to leverage the required spectrum of knowledge, expertise, and network, as detailed in the section entitled “Expertise and resources expected from applicants at stage 1”. Positive results will lead the consortium to make recommendations with regards to wider government run programme(s). Perspectives from Public Partners will ensure that proposed solutions are fit-for-purpose, and truly value-added for all stakeholders. The establishment of a public-private partnership offers a unique mechanism for all parties to engage in delivering the range of input and expertise necessary for achieving the project aims and ensuring that a practical and long-term sustainable plan follows this action.

Scope

It has been recently estimated that between 3.5 to 5.9 % of the general population has a RD (excluding rare cancers) and 72% of those RDs have an identified genetic origin[1]. Therefore, RD genetic screening might yield significant results. In addition, 70% of those RD patients are children [1], which points towards new-born screening[6]. In 2003, the cost of sequencing a human genome was a billion dollars. Today, it is under a thousand dollars. With the advent of gene / genome sequencing, along with the unprecedented availability of digital tools enhancing ways to collect, store, process and interpret massive amounts of data (“big data”), there is an unprecedented opportunity to transform the landscape of RD diagnosis as it is today.

The proposed project addresses the RD conundrum by focusing on shortening the path to diagnosis for RD patients. The overall objective of this call topic is to shorten the path to RD diagnosis by using new-born / paediatric (infants during their first weeks of life) genetic screening; and, via application of advanced digital technologies that enable rare disease suspicion / identification. The latter might require consolidation of existing fragmented efforts.

The specific objectives are:

1. Assessment and development of a comprehensive, strategic overview of existing converging RD resources e.g. databases, registries, natural history projects, platforms, reference networks, rare disease academic centers of excellence, and initiatives for evaluation / identification of potential collaboration and synergies;
2. Federation of available RD databases into a RD metadata repository amenable to machine learning or other advanced digital tools;
3. Co-creating a sustainable strategy for new-born genetic screening and pilot it. This could start directly after the achieving objective 1;
4. Based on the output of objectives 1 & 2:
    a) Repurposing of pre-existing suspicion AI algorithm to identify early onset RD patients in Electronic Health Records. This will include at least 3 pilots in better known rare diseases (with the understanding that solutions and algorithms developed or adapted should be amenable or made amenable to be emulated for larger sets of better known RDs) where more robust data is available to train and test the AI algorithm(s), and / or ;
    b) Design and development of new AI algorithm(s) to achieve the above goal.
5. Based on insights generated by the objectives 1, 2 & 4, either repurposing or development of a broad AI RD suspicion “symptom checker” to help undiagnosed RD patients cycling through health care professionals (HCPs).

[6] https://www.eurordis.org/sites/default/files/publications/fact-sheet-new-born-screening.pdf

In addition, exploration of viable further options to implement the symptom checker in actionable solutions for HCPs and patients.

Expected key deliverables

The consortium would have the following role:

1. Responsible for making it possible to interconnect all the different sources of data;
2. Curate data to make it interoperable and reusable;
3. Ensure the algorithms are compliant with existing/emergent governance and validation policies;
4. Make the algorithms available to the hospitals to run on their existing systems and at the same time use the data generated by the algorithms to improve diagnosis (through prediction; identification of potential new diagnostic/predictive/monitoring biomarkers).

The key deliverables are as follows:

1. Addressing objective 1: All listed deliverables are required in order to perform the subsequent "steps", must include GDPR / data ethics considerations and follow FAIR principles:
    a. Comprehensive landscape analysis of ongoing relevant initiatives & pre-existing resources with strategic recommendations about potential for collaboration. This includes a Cochrane systemic literature review, or equivalent;
    b. Landscape analysis of relevant available data sources with analysis of usability readiness (data integrity, validity, re-consenting requirements, etc.) within the timeframe and budget scope of this project;
    c. Definition of a pre-competitive business model to access rare disease data to purchase, license, or negotiate data sharing agreements. The consortium should be able to either bring the data or insure access to data in a sustainable way with a long-term plan. For the data, as for all background brought into the project, access rights (according to IMI2 JU's intellectual property (IP) policy[7]) should be respected during and after the project (access rights of other beneficiaries and of third parties);
    d. Analysis of regulatory, ethics and data privacy dimension requirements with strategic recommendations for subsequent work packages.
2. Addressing objective 2:
    a. Federating of available RD databases into a RD metadata repository amenable to machine learning or other advanced digital tools;
    b. Co-creating new or identify available pre-existing optimal AI approach / platforms (considering access rights etc.), able to identify early onset rare disease patients. Access rights should be considered not only during but also after the project according to IMI2 JU IP policy;
    c. Integration of platforms with de-identified data and control of access rights for each data point to improve the use of big data analytics by several partners;
    d. Platform interoperability: readiness to integrate and aggregate new data from different sources or operate with other platforms, e.g. patient reported outcomes or biobank databases;
    e. Ensuring adoptability and acceptance of such tools from public, regulators and HCPs by engaging in dialogue with relevant stakeholders.
3. Addressing objective 3:

[7] https://www.imi.europa.eu/apply-funding/general-overview/intellectual-property

a. RD gene panel for the purpose of new-born screening (NBS): List of criteria for inclusion / exclusion in the panel (scientific, technical, sustainable, and ethical) aligned with the overarching goals of action.

b. Fully developed RD genetic NBS protocol (and / or kit), tested and validated, with post-diagnosis planning recommendations (genetic counselling, referral, etc.).

c. As a complementary approach, development of a whole exome sequencing (WES) implementation protocol (with criteria) for infants (up to 1-2 months old) with unexplained symptoms, including all considerations mentioned in the deliverables above. These two sequential approaches should be strategically mapped for implementability and acceptability, according to the opinions of all stakeholders, but also on a case by case basis, driven by family decision (both approaches in b & c should be developed).

d. Post-pilot metrics & data on feasibility, health economics, scalability, improved outcomes for patients; benefits to patients & families. This will contribute to the input feeding into health policy and ethics discussions.

4. Addressing objective 4:

    a. Repurposing and / or development of digital suspicion algorithms trained on the RD metadata repository to be used in Electronic Health Records to continuously screen for patients with early signs of better known RDs and facilitate referral for genetic testing or further testing.

    b. This algorithm should be tested; based on this pilot,recommendations should be formulated for Public Health authorities.

5. Addressing objective 5:

    a. Review and analysis of options for a potential artificial intelligence phenotypic recognition tool (digital “clinical symptom checker” support tool) trained on the federated RD database to help RD patients cycling through HCPs. The intent is that the tool(s) will be publicly available afterwards, open source, with associated HCP training curriculum. The tool should be designed in such a way that it would be used by both HCPs and patients.

    b. In addition, generation of a strategic report regarding potential viable further options to implement the symptom checker in actionable solutions for HCPs and patients. This could include mapping further potential functionalities within the symptom checker and / or other avenues to leverage the symptom checker capabilities.

6. Overall output:

    a. Publication plan, data dissemination and communication plan, recommendations to Public Health governing bodies, multi-stakeholder engagement strategy, including EMA, FDA and other regulatory bodies.

Expected impact

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include, wherever possible, baseline, targets and metrics to measure impact.

The Rare Disease conundrum:

Despite the recent rise in RD Research and Development, most RDs remain under studied, and therefore under treated / cared for. This can be attributed for the most part to:

- Patients are not identified / diagnosed;
- Lack of epidemiology data;
- No natural history of disease data;
- No validated Endpoint / Patient Reported Outcomes (PROs);
- Patient are rare, experts are even more rare.

This has the pernicious additional effect of blunting interest in diagnosis / screening initiatives, as it would lead to patients being diagnosed, with no concrete medical or clinical option. This poses an ethical challenge, which unfortunately feeds the conundrum. This has been identified as a major problem for the rare disease community.

This Call topic anticipates the following benefits:

- For patients:
  - Decreased time to the right diagnosis;
  - Improved patient journey;
  - Better healthcare;
  - Increased quality of life;
  - Decreased irreversible organ damages;
  - Access to their own healthcare data.
- For healthcare
  - Implementation of digital transformation in healthcare;
  - Paradigm change in rare diseases diagnosis;
  - Improved diagnostic tools;
  - Improved understanding of disease;
  - Higher accuracy in clinical decisions;
  - Better care delivery;
  - Integrated care among different specialties.
- For research
  - Advances in utilisation of digital technologies;
  - Increased diseases knowledge for future research;
  - Improved data availability for future research.
- For society
  - Decreased burden for family and carers;
  - Increased trust in the healthcare system;
  - Better use of data for public health;
  - Improved value-based healthcare.

In their proposals, applicants should outline how the project plans to leverage the public private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for the engagement with patients, healthcare professional associations, healthcare providers, regulators, Health Technology Assessment (HTA) agencies, payers etc., where relevant.

In addition, applicants should describe how the project will impact on competitiveness and growth of companies including SMEs.

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards.[8]
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures.[9]
- Communicate the project activities to relevant target audiences.

Potential synergies with existing consortia

[8] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

[9] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[10]) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium plans to contribute the following expertise and assets:

- Project Leadership and Programme Oversight, Genetic Research, Medical Affairs, Data Science/Analytics & AI, Epidemiology, Regulatory, Public Relations / Policy, Commercial Innovation
- Scientific Affairs, Innovation, PPP management support, Medical Affairs, Public Affairs
- Genetic Diseases / Digital Medical Innovation, New-born screening, Diagnostics, Personalised Medicine/Healthcare, Public policy, Immunodeficiencies

One of the foreseeable rate-limiting factors for the success of this project is the availability of robust disease natural history data, of high enough quality that it can be used for machine learning (training data sets). During the funded action, members of the industry consortium plan to contribute scientifically relevant activities for generating data in prospective activities that are part of broader clinical studies independent from, but carried out in connection with, the action and necessary for achieving its objectives. The introduction of the data constitutes an in-kind contribution which entails access rights to these project results in line with IMI2 JU IP rules. The estimated in-kind contribution for the prospective activities to generate these data is EUR 3 500 000.

Data provided by members of the industry consortium will include (but not limited to) rare disease clinical trial data. This data will be either control data (such a placebo) or baseline data. For the purpose of this project, such data will serve as “natural history data”, to be used for machine learning covered by objectives 2, 4, and 5.

The relevant activities will become project activities and as such will have to be included in the project work plan, associated to deliverables and reported. Any results will then be subject to the relevant obligations of the IMI2 IP policy.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture, which could be in line with the suggested architecture described below, though this architecture is only a suggestion.

This may require mobilising, as appropriate the following expertise:

The consortium should include (but not limited to) the following key stakeholders:

- Patient Organization, Academia, SMEs, Public Health Decision Makers, Regulators.

[10] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

The consortium should mobilise the following expertise:

- In order to achieve objective 1 and to deliver associated deliverables, the consortium should have the required expertise and capabilities to networking with EU, local Healthcare & Data Protection Regulators. Expertise will be needed in the fields of regulatory affairs, policy and politics, health economics, HTA / pharmaco-economy, regulatory sciences, legal / IP / licensing, rare disease expertise, international rare disease Patient Advocacy, patient journey, Innovation, public health, expertise in high & low-income EU health systems, public health systems Implementation.
- In order to attain goals described for objective 2, 4 & 5 and to deliver associated deliverables, the consortium should have the required following expertise and capabilities: Data Exchange & Building Digital Infrastructure, User experience, Data security and Data Anonymisation, Methodology development, Data Management, Data Science, Data standards, Data translation, Pharmaco-epidemiology, Biostatistics, Bioinformatics, Software Engineering, Data stewardship, Business and governance model development (Including sustainability), Medical, Legal General Data Protection Regulation (GDPR) Compliance, Data ethics, Privacy, Medical Insurance, Medical Training, Data Quality assurance, IT, Cyber security, Federated data
- In order to attain goals described for objective 3 and to deliver associated deliverables, the consortium should have the required following expertise and capabilities: Genetics, Genomics, Molecular Biology, Whole Exome and Whole genome Sequencing (WES / WGS), Gene panel, In silico panel, Bioethics, Genetic Counseling;
- In addition, the following general expertise / capabilities will be required: Project Management, Study / Trial Operation Manager, Medical / Scientific Writing, Communications, Public Outreach.

It may also require mobilising, as appropriate, the following resources:

- Ideally, the consortium should welcome the participation of partners who could and would be willing to contribute RD phenotypic data that could be integrated in the meta-data repository that would train the AI algorithm(s), as well as partners able to contribute pre-developed rare disease recognition algorithm(s).

Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal;
- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/ HTA settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

Work packages:

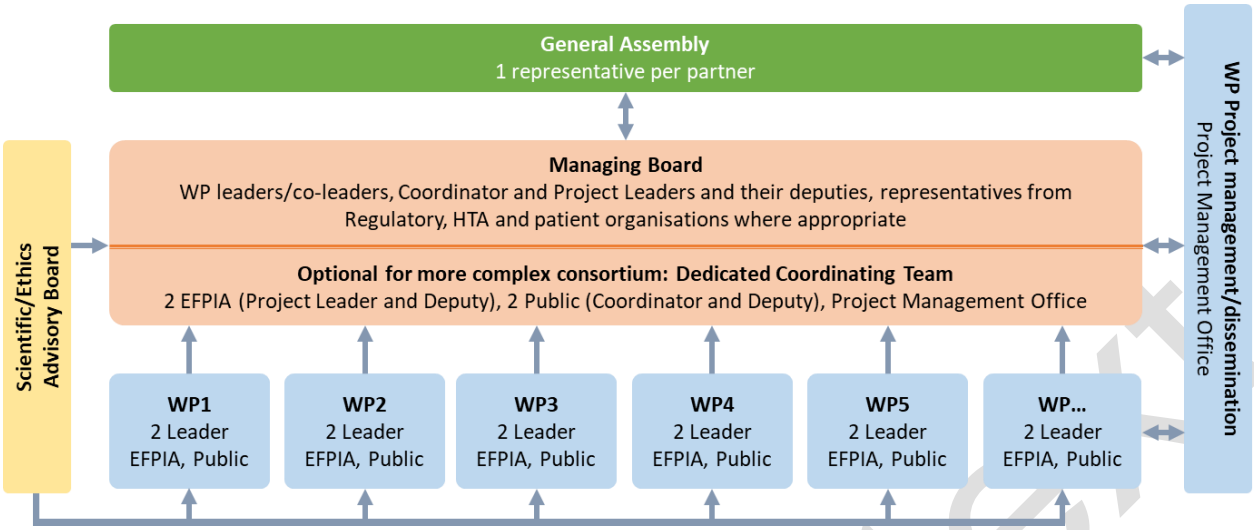
It is suggested that each of the 5 objectives described under section "SCOPE" (with associated goals and deliverable) becomes a work package (WP).

In addition, consideration should be given to a project management WP that would:

- Ensure alignment between the participants as well as smooth internal and external communication;
- Monitor compliance with the work plan;
- Monitor planned resources and time schedule;
- Coordinate fulfilment of all administrative milestones;
- Ensure legal and data privacy requirements are met during the project lifetime.

Applicant consortium is expected to contribute to project management, ensuring the implementation of the coordinating tasks and running the day-to-day operation, such as project tracking and reporting, meetings, internal communication, website creation, budget management, etc.

Example Architecture:



Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.[11]

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project[12], and updated during the project lifetime and could include identification of:

- Different types of exploitable results;
- Potential end-users of the results;
- Results that may need sustainability and proposed sustainability roadmap solutions.

[11] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

[12] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).[13]

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

References

[1] Nguengang Wakap, S., et al., Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet, 2020. 28(2): p. 165-173.

[13] http://www.corbel-project.eu/about-corbel/research-infrastructures.html